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EXAMINER	
BRUSCA, JOHN S	
ART UNIT	**PAPER NUMBER**
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,942	CAMPBELL ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15,18-30 and 128-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-15,18-30 and 128-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. The objection to claim 30 in the Office action mailed 26 January 2007 is withdrawn in view of the amendment filed 26 July 2007.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must assay for the effect of a peptide library on alteration of production of antibiotics, steroids, carbohydrates,

lipids, and nucleic acids in cultured cells. For the reasons discussed below there would be an unpredictable amount of experimentation required to use the claimed method.

b) The specification does not present specific guidance for practicing the claimed method.

c) The specification does not present working examples of the claimed method.

d) The nature of the invention, screening of the effect of peptide libraries, is complex.

e) Lam et al. shows a method of screening peptide libraries for production of a desired effect in cells. Lam et al. does not show peptides that affect production of antibiotics, steroids, carbohydrates, lipids, and nucleic acids in cultured cells. A search of the prior art did not reveal use of peptides to alter production of antibiotics, steroids, carbohydrates, lipids, and nucleic acids in cultured cells.

f) The skill of those in the art of cell culture assays is high.

g) The prior art does not predict whether the claimed method can be used.

h) The claims are broad in that they are drawn to a method without experimental support that shows that it can be used.

The skilled practitioner would first turn to the instant specification for guidance in practicing the claimed method, however the specification does not provide such guidance. The skilled practitioner would next turn to the prior art for such guidance, however the prior art does not show such guidance. Finally, said practitioner would turn to trial and error experimentation to practice the claimed method. Such represents undue experimentation.

4. Applicant's arguments filed 26 July 2007 have been fully considered but they are not persuasive.

The applicants have failed to provide any evidence or arguments that the claimed subject matter of claim 30 can be **used** by one of skill in the art, and the rejection under 35 U.S.C. 112, first paragraph is maintained. The applicant's arguments regarding the Wands factors are rebutted as follows:

A) The quantity of experimentation necessary: the applicants merely state that experimentation that is not undue is permissible, however the experimentation required is unknown since no guidance or examples are provided by the specification. There is no indication in the combination of the specification and the prior art that the claimed subject matter can be practiced with success or that the claimed subject matter can be used.

B) The amount of direction or guidance presented: The applicants state that explicit guidance is not required, without showing how the specification or prior art enable the claimed subject matter.

C) The presence or absence of working examples: The applicants state that a working example is not required, without showing how the specification or prior art enable the claimed subject matter.

D) The nature of the invention: The applicants agree with the Office that the nature of the invention is complex.

E) The state of the prior art:

F) The relative skill of those in the art:

G) The predictability of the art:

Regarding factors E, F, and G, the applicants state that the specification enables performing assays without providing evidence that useful results of the assays could be obtained.

H) The breadth of the claims: The applicants state that the specification need not support the breadth of the claims without showing how the specification enables the claimed subject matter.

After weighing all Wands factors, the Office has concluded that claim 30 is not enabled for the reasoning detailed above. The applicants have not presented evidence or reasoning why one of skill in the art could make and use the claimed subject matter of claim 30, and the rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-10, 13-15, 18-28, and 128-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al. in view of Zheng et al. in view of Bause as evidenced by Invitrogen catalog.

The claims are drawn to a method of characterizing (including space-filling design methods) and screening a first library of compounds by assaying the effect of members of the library in culture medium by measuring an effect of the compounds on the properties of the media. The property of the medium is correlated with a property of the compound. A second library of compounds not present in the first library of compounds that meets a predetermined range of properties as assessed in the first screen is then constructed and screened in media. The second screen is used to select a culture medium component with desired properties. In some embodiments the property of the medium is a function of the property and the compound assayed. In some embodiments the second screen includes compounds analyzed by space-filling techniques. In some embodiments the property of the compound is sequence-specific, a whole molecule parameter, or a molecular weight. In some embodiments the compounds are peptides with at least one residue of limited variability. In some embodiments the medium is seeded with mammalian cell cultures and a property of the medium is growth of the cell culture or altered peptide or protein production. In some embodiments the culture medium is a synthetic medium. In some embodiments the first and second screens are done on compounds that do not have fully random sequences. In some embodiments the first screen is done on compounds with a fully random sequence. In some embodiments the first screen is done on a portion of the library that represents the full diversity of the library.

Lam et al. shows in columns 21 and beyond assays of random peptide libraries on beads added to cells in growth media. The peptides are released from the beads to the media and the cultures are assayed for modulation of growth or other parameters. Lam et al. shows a second round of screening of variants of the first library in column 17 lines 18-24. Lam et al. shows

assay of cytokine release (a polypeptide) from assayed cultures in column 22 line 60 to column 23 line 3, and measurement of toxicity in column 23 lines 3-14, and screening for peptide inhibitors of tumor cell growth in column 45-46. The sequence (and therefore the molecular weight and structure of the entire peptide) is assayed in columns 27-28. Multiple properties of the peptide library are detected in the examples in columns 41-46. Insertion of non-variable residues in the random peptide sequence is shown in column 8, lines 30-32 and column 40. Lam et al. shows use of fully random peptide libraries in columns 8-14 and 34-35. Lam et al. shows use of peptide libraries that are partially random with partially predetermined sequences in column 24, line 28-45 (exclusion of cysteine), columns 40-43 (only 14 amino acids present), and column 11, lines 8-30 (general guidance for use of partially random peptide libraries). Lam et al. shows in columns 37-39 and example in which a subset (two million beads) of the library of random peptides is assayed, in which the sample is a representative sample of the total possible random peptides in the library. The results of the assays show that the property of the medium is a function of the particular peptide in the medium. Lam et al. shows use of RPMI medium in column 45, but does not show that RPMI medium is a synthetic medium. Lam et al. does not show use of space-filling analysis to measure properties. Lam et al. does not show determination of parameters of the first library before screening, or of determining functions of quantitative structure activity relationships (QSAR) analysis.

Invitrogen catalog shows the content of RPMI medium. Invitrogen catalog shows that RPMI medium consists entirely of defined compounds.

Zheng et al. shows in the abstract and throughout a method of constructing and refining a peptide library by use of QSAR analysis. Zheng et al. states in the abstract that their method

allows for construction of libraries that are most likely to have a desired activity. Library members are selected by use of a pre-constructed QSAR equation. Figure 1 shows that the method can be iterative to different libraries, as further illustrated in the discussion of library optimization on pages 4-6.

Bause shows analysis of peptide sequences that are sites of glycosylation can be aided by consideration of space-filling parameters in figures 2-4 and pages 333-335.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ space-filling techniques to analyze the selected peptides of Lam et al. because Bause shows that such analysis is useful to determine properties of peptides. It would have been further obvious to use the QSAR methods of Zheng et al. to characterize a first and second library because Zheng et al. shows that such analysis allows for selection of library members that are most likely to have a desired activity.

8. Claims 11, 12, and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al. in view of Zheng et al. in view of Vyas et al.

The claims are drawn to a method of characterizing (including space-filling design methods) and screening a first library of compounds by assaying the effect of members of the library in culture medium by measuring an effect of the compounds on the properties of the media. The property of the medium is correlated with a property of the compound. A second library of compounds not present in the first library of compounds that meets a predetermined range of properties as assessed in the first screen is then constructed and screened in media. The second screen is used to select a culture medium component with desired properties. Claims 11

and 12 are drawn to use of isomers of compounds and space-filling analysis in the method of claim 128.

Lam et al. shows in columns 21 and beyond assays of random peptide libraries on beads added to cells in growth media. The peptides are released from the beads to the media and the cultures are assayed for modulation of growth or other parameters. Lam et al. shows a second round of screening of variants of the first library in column 17 lines 18-24. Lam et al. shows assay of cytokine release (a polypeptide) from assayed cultures in column 22 line 60 to column 23 line 3, and measurement of toxicity in column 23 lines 3-14, and screening for peptide inhibitors of tumor cell growth in column 45-46. The sequence (and therefore the molecular weight and structure of the entire peptide) is assayed in columns 27-28. Multiple properties of the peptide library are detected in the examples in columns 41-46. Insertion of non-variable residues in the random peptide sequence is shown in column 8, lines 30-32 and column 40. The results of the assays show that the property of the medium is a function of the particular peptide in the medium. Lam et al. shows use of RPMI medium in column 45, but does not show that RPMI medium is a synthetic medium. Lam et al. does not show use of space-filling analysis to measure properties or use of compound isomers. Lam et al. does not show determination of parameters of the first library before screening, or of determining functions of quantitative structure activity relationships (QSAR) analysis.

Vyas et al. shows that the structure at the amino terminus of a particular peptide is important for receptor binding in the abstract and throughout. Optical isomers of peptides are studied on page 3608 to analyze the binding activity of the peptide. Space filling parameters of peptides are shown in figure 5 to further study structural requirements of binding activity.

It would have been further obvious to use the QSAR methods of Zheng et al. to characterize a first and second library because Zheng et al. shows that such analysis allows for selection of library members that are most likely to have a desired activity. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ space-filling techniques and peptide isomers to analyze the selected peptides of Lam et al. because Vyas et al. show that such analytical techniques are useful to study relationships between peptide structure and activity.

9. Claims 19, 23, 28, 29 and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al. in view of Zheng et al. in view of Bause as evidenced by Invitrogen catalog as applied to claims 2-10, 13-15, 18-28, and 128 and further in view of Davis et al.

Lam et al. in view of Zheng et al. in view of Bause as evidenced by Invitrogen catalog as applied to claims 2-10, 13-15, 18-28, and 128 does not show the effect of a library of compounds on toxin production.

Davis et al. shows on pages 685-686 that Corynebacterium diphtheriae toxin is a polypeptide. Davis et al. show throughout that toxin causes a serious disease in humans by blocking protein synthesis.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Lam et al. in view of Zheng et al. in view of Bause as evidenced by Invitrogen catalog as applied to claims 2-10, 13-15, 18-28, and 128 to determine the effect of a library of compounds on toxin production because Davis et al. shows that Corynebacterium diphtheriae toxin is a polypeptide that causes a serious disease in humans and modulation of toxin production would modulate disease in humans.

10. Applicant's arguments filed 26 July 2007 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicants state that the claimed subject matter was misconstrued in the rejection because the claims require the second culture medium to have an estimated indicia, however Lam et al. shows a second round of screening using previously characterized peptides that would provide an estimate of the effect in the second round. The applicants state that Lam et al. does not show a quantitative structure function relationship. Zheng et al. shows precharacterization and quantitative structure activity analysis as discussed above. The applicants state that Lam et al. does not show a second test library that is composed of members that are not in the first test library, however Zheng et al. shows QSAR analysis that facilitates analysis of compounds not experimentally characterized by allowing for prediction of the activity of compounds. The applicants state the claimed subject matter assays an unbiased sample of compounds while Zheng et al. shows selection of compounds for desired properties. The claims do not require unbiased samples for assay in the test libraries, and the first test library is explicitly claimed as biased in new claim 129. The applicants state that the applied references are from non-analogous arts, however the applied references are all from the peptide analysis art and the claimed subject matter is broader than peptide analysis.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/
Primary Examiner
Art Unit 1631

jsb